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Article

Immunological and Cytokine Profiling in Ulcerative Colitis: Focus on IL-10, IL-37, IFN-γ, and CD8+ T Cell

Ali N. Hamid
Department of Medical Microbiology, College of Medicine, University of Al-Qadisiyah, Iraq

Supervised by: Dr. Israa Abdulwahid Dheeb
College of Medicine, University of Al-Qadisiyah, Iraq

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*Correspondence: med.post25.17@qu.edu.iq

Abstract: Ulcerative colitis is one among the most prevalent forms of inflammatory bowel diseases. The hallmark of this condition is an abnormal immunologic response that gives rise to chronic inflammation of the colonic mucosa. The current literature on this subject will be discussed in this article, which will have a focus on reviewing and analyzing recent literature published between 2021 and 2025. Research has found that a breakdown of the epithelial barrier and change in gut microbiome result in an imbalance between the innate and adaptive immune systems due to excessive levels of inflammatory cytokines like IFN-γ and reduced levels of regulatory mediators IL-10 and IL-37. Data have also recently pointed towards the role of CD8+ T cells in perpetuating inflammation. Despite progress made by available medications such as 5-ASA, steroid therapies, biologics, and JAK inhibitors, there is a need for new approaches focusing on molecular fingerprinting and immunoadaptation due to current treatment incompliances and relapse. The future trends point towards enhancing research in the country and national registries for UC patients to design treatment courses in line with demographic- and environment-related features of Iraq.

Keywords: IFN-γ, IL-10, IL-37, Inflammatory bowel disease , Ulcerative colitis.

Introduction

Ulcerative colitis (UC), which has been described as a "chronic inflammatory condition involving the mucosa of the colon" or rectum, "is considered to belong to a group of conditions classified generally as inflammatory bowel diseases" that are "of autoimmune origin. "[1]. Its spread is estimated to be increasing in a number of areas globally. Infection increases are posing greater pressure to health services [2]. There are a few predisposing causes which contribute to its development. These are genetic causes, alteration in the function of the intestinal barrier, imbalance in the gut microbiota, along with an irregular immune response that causes damage to colonic tissue. (Yuqing Liang et al., 2024). Recent studies suggest that the proportion between immune cells that are acquired or innate to the organism, and between pro- or anti-inflammatory cytokines, plays a crucial role in understanding the progression of diseases [3]. Although there has been great improvement in conventional and

biological therapy, there is still a challenge due to high relapse rates and a lack of complete control of the disorder. [4]. Accordingly, the scope of this review will be to collate and interpret published literature since 2021 related to immune cells like CD8 and specific interleukins like IL-10, IL-37, and IFN-γ in association with UC. Such focus is crucial in recognizing gaps in knowledge as well as areas to focus on in future studies which can address the Iraqi context [5]. These topics include epidemiology and predisposing factors, pathogenesis, cytokine networks, diagnosis and clinical manifestations, treatment options, and finally recommendations [6].

Epidemiology and Predisposing Factors

Recent literature suggests that there is a growing burden of inflammatory bowel diseases globally, with a differing rate of development across various geographic areas, and that ulcerative colitis contributes substantially to this burden [7]. In fact, the center of gravity within epidemiology is shifting away from Western nations to newly industrialized nations with increasing needs for diagnosis and treatment. In MEA, there appears to be a steady increase in the incidence or prevalence of IBD. In fact, there are signs that a similar trend in UC appears to be emerging in those countries [8]. Research focusing on the burden of diseases in the Middle East and North Africa highlights a growing burden along with differences across the country due to various environmental, economic, and health-related elements [9]. Urbanization or changes in eating patterns to processed or low-fiber diets could potentially raise susceptibility to developing IBD due to changes in gut microbiota or mucosal barriers [10]. Recent microbiota literature confirms that imbalance between diversity and homogeneity for bacteria represents an indicator for progression of mucositis symptoms and disruption of homeostasis in UC patients [11]. The genetic component represents a continually acting factor. The most recent reviews demonstrate that there are over 240 susceptibility loci for genetic predisposition to IBD identified for both innate and acquired immunity [12]. More recent studies using genetic or epigenetic data indicate that gene-environment interactions are involved in inter-population variation in risk [13]. Modern studies validate the microbiome's role as an important intermediary between environment and immune system with evidence supporting its dysfunction in UC patients and its emergence as a therapeutic target [14]. Specialized reviews emphasize the possible role of diet components and microbial metabolic processes in determining susceptibility to relapse or severity of symptoms due to short-chain fatty acids or tryptophan metabolites. [15]. In terms of health planning, there are contemporary global data analyses which address combined prevalence and incidence data for both IBDs and UC [16]. Unlike these, there are some health systems that have shown signs of stability concerning indicators compared to areas that are experiencing growth in terms of epidemiology [17].

Pathogenesis

Ulcerative colitis was recently found to result from a complex interplay between genetic predisposition and environmental factors. Indeed, there was confirmation for a model involving a relationship between epithelial barrier function, the immune system network, and microbiota [18]. Epithelial barrier disruption presents features like increased barrier permeability, disruption of tight junctions, and passage of antigens. It was confirmed in recent reviews that barrier dysfunction plays a pivotal role in both initiation and maintenance phases of inflammation in patients with IBD, including those with UC [19]. The mucous layer/goblet cells are a crucial component of the first line of defense. The mucous defect/goblet cells are related to chronic mucous membrane inflammation in UC. Impaired mucous clearance makes the immune system more vulnerable to microbes and leads to increased susceptibility to inflammation [20]. Dysbiosis of gut microbes refers to both reduced commensal bacteria that produce SCFAs and elevated pro-inflammatory bacteria. These two conditions interact with barrier dysfunction. As a consequence, there is a need for a therapy that targets microbes [21]. Research involving microbiome composition has shown that there are differences in UC patients' microbiota compared to those who are healthy. These differences can be used to define diagnostic criteria or indicators. Such differences are observed based on various stratification criteria [22]. At the immunological level, the trigger starts with microbial molecular pattern recognition in innate immune receptors, which leads to NF-κB activation/MAPK pathways and subsequent cytokine secretion. The spectrum continues to encompass an induced response in which T and B lymphocytes are involved in an imbalance to achieve stability within the inflammatory condition [23]. Macrophages and dendritic

cells serve as a connection between innate and adaptive immunity based on antigen presentation and T-cell differentiation. As a result, in UC, the imbalance observed in activation and polarity in these cells increases the inflammatory response [24]. Activation of NLRP3 inflammasomes correlates with short-chain fatty acid insufficiency. It causes impairment in homeostasis, which results in mucosal barrier damage. Also, there is aggravation of inflammation. The triad occurs as a connection between microbiota aberration and mucosal inflammation [25]. Imbalances between Th17 and Treg cells are considered one of the pivotal pathologic axes. High levels of Th17 cells and reduced Treg cells perpetuate an inflammatory condition in the mucosa. These conditions are related to more active clinical courses. Moreover, there are increased episodes [26]. Microbiome-targeted therapeutic procedures like fecal transplant could potentially address this imbalance through increased Treg numbers and reduced Th17 signalling. These are areas that have clinical and immunological basis to prove its association between microbiome function and immunity in UC [27]. Genetic predisposition and epigenetic susceptibility result in a burden with reference to loci involved in innate immune pathway recognition mechanisms, T-cell differentiation pathways, and cytokine regulation. These interactions shape susceptibility to environment exposures [28]. Indeed, an integrated approach typified in UC describes the condition as a barrier-microbiome-immune system dysfunction. As a result, there are several treatment methods targeting these pathways. These are evident in emerging treatments [5].

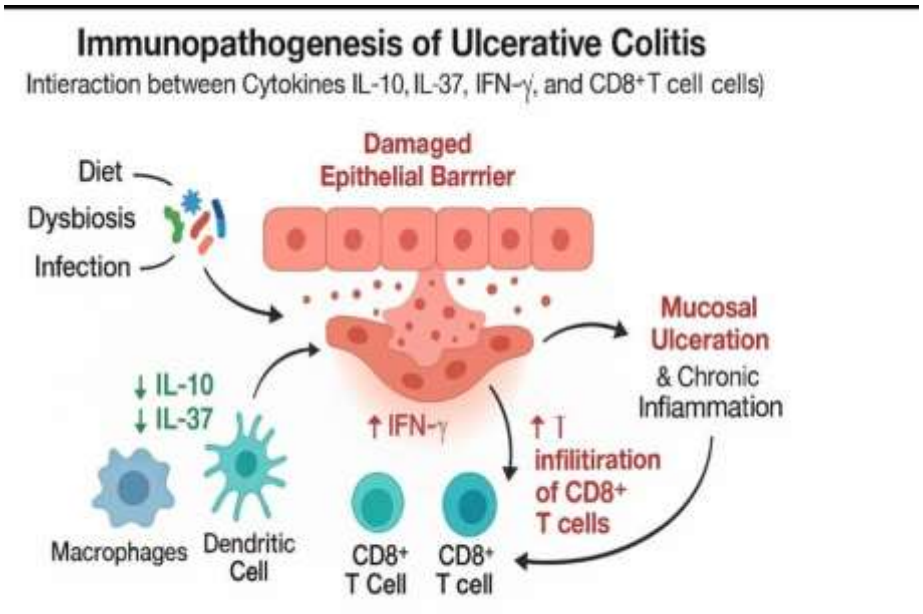

Figure 1. Immunopathogenesis of Ulcerative Colitis, interaction between cytokines (IL-10, IL-37, IFN-γ), and CD8+ T cells.

The Cytokine Network in Ulcerative Colitis

Cytokines constitute a complex interlocking system that regulates the balance between pro- and anti-inflammatory reactions in colonic mucosa. In ulcerative colitis (UC), there's an imbalance in favor of an unremitting inflammatory response with specific therapeutic targets [6]. Contemporary system-level studies show that "communication maps" between cytokines in UC are identified with characteristics that are specific to subtypes in patients who are not treated with drugs [29]. Recent reviews suggest that the pathways involving IL-1β/IL-6/IL-23 and TNF-α interact with counter-regulatory signals like IL-10 to regulate both the severity of inflammation and recurrence. These observations are helpful for developing treatment strategies that regulate these pathways rather than focusing on individual agents [6]. Data regarding clinical immunology further illustrate that the

cytokine network responds to treatment approaches altering disease courses, with emerging choices extending to IL-23/JAK inhibitors in UC [30].

Interleukin-10 (IL-10)

IL-10 is a major mucosal homeostasis regulator that negatively regulates both antigen presentation and inducing cytokine secretion. In contrast, JAK1/TYK2-STAT3 signaling occurs through a tetrameric receptor (IL-10Rα/β). The abrogation of IL-10/IL-10R interactions causes severe enteritis very early [31]. Mouse studies demonstrate that the absence of IL-10 leads to chronic colitis with cellular infiltration and augmented barrier permeability, thus further emphasizing its pivotal anti-inflammatory function in the colonic mucosa [32]. At a clinical level, there are correlations between IL-10 and markers of both disease activity and nutrition in patients with IBD, thus informing its use as an aid biomarker [33]. There are emerging reports of the existence of IL-10-neutralizing autoantibodies. These are considered to potentially offer therapeutic benefits [34].

Interleukin-37 (IL-37)

IL-37 is a broad-spectrum inhibitory cytokine whose function is to control inflammatory gene expression. There are human observations that a gene defect in IL-37 leads to severe childhood-onset ulcerative colitis [35]. Open-label reviews indicate that IL-37 plays a role in regulating mucosal immunity both systemically and locally with interactions with NF-κB and MAPK pathways. In experimental researches, it was shown that the involvement of IL-37 could be influenced by microbiota conditions since its overexpression could mean protective effects in pathogenic conditions but could enhance inflammation in conditions influenced by microbiota culturing. The role seems to depend upon the "microbial environment" [36]. Recent regional data shows its possible use as a biological marker for IBD based on differences in its level between patients and healthy people, which demand further confirmation studies [37].

Interferon-gamma(IFN-γ)

IFN-γ represents a prominent pro-inflammatory mediator activated through the STAT1 pathway and impacts vascular and epithelial barrier function with increased expression demonstrated in UC mucosa compared to normal subjects [38]. Recent reviews show that targeting IFN-γ signaling pathways, which are currently being explored, can lower disruption of adhesions and septal damage [39]. IFN-γ sits atop a complex pathway involving the IL-12/23 pathway and regulators of Th1/17 cell differentiation. Its integration into vascular-mucosal pathology in the colon makes “circuit modulation” instead of blockade a fitting approach [40]. "Systems-level" analysis also shows IFN-γ relationship maps to other mediators in UC. These data suggest possible use in both diagnosis and prediction [41].

The Cytokine Network and connection to Th17/ Treg Balance

An imbalance between Th17/Treg cells is a characteristic feature of UC. High numbers of Th17 cells but fewer Tregs create a pro-inflammatory microenvironment that tends to result in high relapse incidence. A recent systematic review highlights the mechanisms involved in targeting the pathway [42]. It discusses contemporary metabolic/nutrition interactions which shape or regulate Th17/Treg differentiation pathways. It opens a window for therapeutic interventions based on nutrition/metabolism [43].

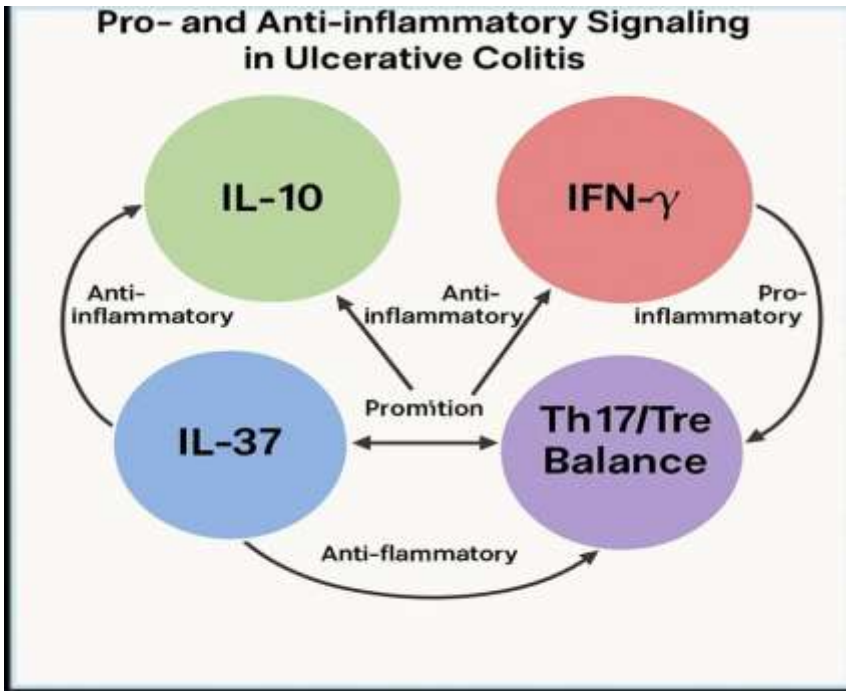

Figure 2. Cytokine interaction network showing both pro-inflammatory and anti-inflammatory pathways involved in ulcerative colitis. Here, IL-10, IL-37, IFN-γ, and the imbalance between Th17 and Treg contribute to conditions leading to ulcerative colitis

Therapeutic implications

The increasing knowledge of the mechanism lends credibility to targeting therapies like IL-23 antagonists, JAK inhibitors, and emerging immunomodulators targeting UC-related immune pathways. There are debates, though, whether these agents improve treatment options or merely raise costs. Recent reviews agree that options are increasing according to cytokine profiles [4]. Network mapping platforms suggest that there could be an "opportunity to detect response patterns" which could enable "identification of a specific drug target" per individual [29].

Diagnosis and Clinical Manifestations

The bloody diarrhea with urgency and pain is the hallmark symptom in UC, and the extent to which inflammation is involved is correlated with symptom severity [44]. It can occur with symptoms such as arthritis, inflammation of the eyes and biliary tract, and can even precede symptoms of the intestine [45]. Laboratory evaluation involves CBC, CRP, and ESR. These are used for assessing inflammatory activity [46]. Fecal calprotectin is a useful non-invasive test for differentiation, monitoring, and tracking mucosal healing [47]. The definitive diagnosis and extent can only be made by means of colonoscopy with biopsy [48]. The biopsy reveals a chronic pattern of mucositis with goblet cell depletion and architectural disturbances related to disease activity [49]. CT/MR scans can be used for the intestines if there is difficulty with endoscopy or for identifying complications such as toxic megacolon [50]. Recent literature has summarized the following: features of serious acute seizures, and approaches to initial assessment and advanced treatment [51]. The Montreal classification is used for staging purposes concerning the determination of extent (E1-3) and clinical severity (S0-3) [52]. These newly developed schedule types have been adopted in clinical and educational practices. They are used in accordance with regional guidelines [53]. The guidelines promote screenings for colorectal cancer 8-10 years following the onset of metastatic disease, then individualized surveillance based on risk factors [54]. Recent literature highlights the role of periodic follow-up with advanced endoscopy every 1 to 3 years for detection of dysplasia [55].

Therapeutic Approaches & Recent Advances

Treatment regimens for Ulcerative Colitis typically involve starting with inhibitors such as 5-ASA or steroids, based on the severity and extent of symptoms, and then followed by immunotherapy or biologics in moderate to severe disease [56]. Recent guideline recommendations have emphasized that it is necessary to consider patient history, prior response rate, and related factors for deciding on treatment [57]. The treatment involving TNF-α antagonist or IL-23 antagonist has recently been incorporated in the management of patients who have failed to respond to conventional treatment, with considerable improvement in both incidence and maintenance. An extensive literature review in 2024 revealed that innovative drug marketers have succeeded in obtaining better response rates with good safety acceptance than before [58]. In severe situations of UC, IV steroids are continued, but then alternatives such as JAK inhibitors and a switch to a biologic can be considered [59]. Recent evidence implies that a structured treatment course following "circuit-modulation" strategies instead of blocking a solitary mediator might have beneficial effects on long-term clinical outcome [60]. These would include novel therapies for such subtle immunologic changes as modifications in the microbiome, gene therapies, and fecal transplants, which would represent emerging strategies for managing the underlying elements of this disease [61]. According to recent research, the merge between predictive models and biodata constitutes a revolution for personalized medicine because it shortens trial periods [62]. Finally, it is important for Iraqi researchers to note that genetic, environmental, and microbiome variations in this population mean that implementation for these treatments or guidelines might have to be modified for the particular environment in which their patients exist.

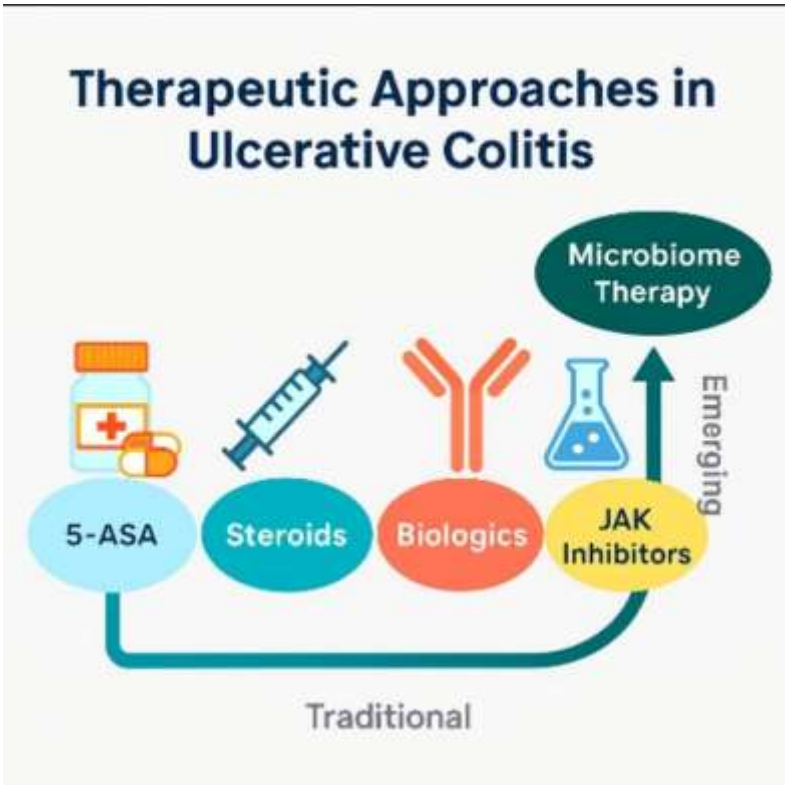

Figure 3. Treatment modalities for ulcerative colitis, signifying the shift from conventional therapies (5-ASA, steroids, biologics) to novel approaches targeting the immune system and the microbiome.

Materials and Methods

Despite progress made in research about ulcerative colitis, a definitive cure for it has yet to be found. Recent literature suggests that controlling or managing it is still a problem [63]. This is a double disadvantage because it is a disease that is seldom investigated in a local setting (such as in the Middle

East or Iraq) with genetic and environmental variations, which makes it even harder to generalize findings [64]. Detection for biomarkers is limited, and this is revealed by a survey study that found that addressing genetic, functional, and analogical links between molecules and patients is only in the beginning stages [65]. Despite current understanding about the role of the microbiome, barrier function, or immune system in UC, there is obvious incompleteness in conceptual knowledge about this subject, which has been revealed by analytical research [66]. The implementation process for personalized medicine with algorithms and big data is only in its infancy, and it is evaluated by the 2025 review for technological and implementation issues related to this transition [67]. It is advised that a national or regional registry (in this case, for Iraq), which involves immunologic, genetic, and microbiome information, needs to be established to facilitate research and forecasting for complications in this particular setting [68].

Results and Discussion

Recent evidence has confirmed that a dysfunctional immunological imbalance exists in ulcerative colitis patients, with regard to the inflammatory response axis and cytokines. A literature search completed between 2021 and 2025 reveals an imbalance between the anti-inflammatory cytokines IL-10 and IL-37, and the pro-inflammatory cytokines, specifically IFN-γ, as an important driving force in maintaining the chronic colonic mucosa inflammation seen in this condition. A lower level of Interleukin-10 results in decreased regulation of the immune response, hence a greater number of active cells secrete greater quantities of TNF-α and IL-6, leading to a higher relapse rate and severity of the disease. However, a positive relation between IL-10, nutritional status, or level of disease activity makes IL-10 a good biomarker, as indicated by some studies. Interleukin 37 plays a dual role as a function of microbial environments, acting as an inhibitor of the inflammatory gene response by suppressing the pathways of both NF-κB and MAPK, while other studies propose that its overexpression, given an imbalanced microbial condition, may enhance the gene response, hence implying that its effectiveness is condition-based, relying entirely on the microbial status of the body, hence the rationale that each immunotherapy should be coupled with a microbial balance approach. On the other hand, studies have found that high levels of Interferon-γ are related to an increase in epithelial permeability and damage to the mucosa, and that the inhibition of the STAT1 pathway could reduce tissue damage and enhance healing. The feedback cycle between IFN-γ and the IL-12/23 pathway explains why both Th1 and Th17 lymphocyte subsets remain activated and why the disease became chronic. Starting with the immune cell component, an increase in CD8+ T cells has been found to be coupled with an increase in the production of IFN-γ, among other cytokines, signifying their involvement in the attack against the epithelial layer, as well as the maintenance of the autoimmune response. The relative decrease in the level of Treg and IL-10 producers affects the suppression of the inflammation by the immune system. The results are consistent with the current understanding of the molecular basis of UC as an "immunity disorder" arising out of a "dysfunction of the integration between the microbiome, the epithelial barrier, and the mucosal immune system." However, their significance should be appreciated in the broader perspective regarding the utility of IL-10, IL-37, and IFN-γ as markers, and the development of therapeutic strategies targeting this "immune circuitry" rather than an individual "pathway" or "node" thereof. It may be hypothesized, given this discussion, that the immune profile of patients with ulcerative colitis may be affected by certain genetic and environmental components, as far as the Iraqi scenario is concerned, hence the need to conduct future studies to quantify the aforementioned immune components among other relevant parameters.

Conclusion

Ulcerative colitis is a chronic autoimmune disease involving interactions between genetic, environmental, and microbiome components, which ultimately result in an impaired intestinal barrier and a pro-inflammatory cytokine environment, such that a cure is considered a goal that is yet to be attained [69]. Although current treatment can now control symptoms and lower relapse rate in patients to a degree, incorporating strategies informed by cytokine or biological signatures might enhance treatment efficiency and minimize adverse effects [56]. The future role of research is critical to fill these

gaps, including working on biomarkers for clinical use, functional analyses for the microbiome, and clinical trials in a local environment like Iraq to adjust recommendations based on population and environmental variables [25]. Finally, for serious and drug-resistant cases, there is a need for graduated treatment protocols and multidisciplinary surveillance with a focus on recent research findings integrated into local protocols with structured data in Iraq [70].

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